DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review

NDA: 21-290

Sponsor: Actelion Ltd.

Submission: Original NDA for the use of bosentan in the treatment of pulmonary hypertension.

Review date: July 11, 2001

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: Bosentan is clearly effective in the treatment of pulmonary hypertension. Whether it should be approved for use in primary pulmonary hypertension, secondary pulmonary hypertension, both, or neither depends upon the value one places on a symptomatic benefit appreciable only in the aggregate population, compared with various risks, including some not discernible in a small population.

Distribution: NDA 21-290

HFD-110/Project Manager

HFD-110/Stockbridge

HFD-710/Lawrence

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HFD-860/Robbie

This review is based upon primary reviews by Drs. Koerner (pharmacology), Robbie (biopharmaceutics), Gordon (medical), and Lawrence (statistical).

Bosentan is an endothelin receptor antagonist, with about 2-fold higher affinity for ET_A receptors than for ET_B. The effect of endothelin receptor antagonism is a reduction in systemic and pulmonary vascular resistance.

Animal toxicology testing was performed at high multiples of the proposed dose in man. Findings included hepatic enzyme elevations (reversible upon discontinuation), obstructive hepatotoxicity, anema (thought to be related to reduction in vascular permeability), testicular tubular atrophy, and oligospermia[1]. Bosentan was teratogenic and fetotoxic, findings shared with other endothelin receptor antagonists. Bosentan was not genotoxic. Final assessment of carcinogenicity is pending.

The proposed indication is for the treatment of primary pulmonary hypertension. There is an ongoing development program in congestive heart failure.

Bosentan is about 50% orally bioavailable; at the maximum recommended dose, food has no significant effect on bioavailability. Circulating bosentan is largely bound to albumin. Bosentan is extensively metabolized by CYP 3A4 and 2C9. One of the metabolites contributes an estimated 20% to the overall activity. Metabolites of bosentan appear mostly in bile. Use in patients with even mild hepatic impairment is contraindicated.

[1] *Testicular effects have been reported for other drugs with a similar mechanism of action.*

Bosentan is a significant inducer of CYP 3A4 and 2C9, resulting in predictable effects on its own metabolism (50% reduction in steady-state plasma levels) and that of other drugs.

Studies of pharmacokinetic interactions yielded results commensurate with the metabolism studies. Cyclosporine and ketoconazole significantly increased plasma levels of bosentan. Warfarin, simvastatin, and glyburide lowered plasma levels of bosentan. Digoxin, losartan, and nimodipine had no interactions with bosentan.

Most of what is known about pharmacokinetics of bosentan came from studies of normal volunteers. Subjects with PPH had a clearance of 3.8 L/h, compared with 9 L/h in normal subjects.

The sponsor performed two studies to demonstrate clinical benefit to treatment of pulmonary arterial hypertension. Subjects could have pulmonary hypertension of unknown etiology (about 2/3 of subjects) or secondary to connective tissue or autoimmune diseases. They were WHO class III-IV, treated with vasodilators, diuretics, digitalis, or anticoagulants, as needed. Moderate elevations in hepatic enzymes or anemia were exclusions. Both studies evaluated 6-minute walking distance as the primary end point and a variety of symptom, functional status, and outcome variables as secondary end points. Both trials were parallel and placebo controlled. The first (Study 351) enrolled 32 subjects and randomized 2:1 to bosentan 125 mg bid or placebo, and the other (Study 352) randomized 213 subjects 1:1:1 to bosentan 125 or 250 mg bid or to placebo. The duration of randomized treatment was 12 (Study 351) or 16 weeks (Study 352); subjects randomized to bosentan received 62.5 mg bid for the first 4 weeks.

There were few deaths or other reasons for discontinuation from these studies, so the analyses are fairly insensitive to how such subjects are handled, and treatment groups were reasonably well matched for demographic and baseline characteristics. Both trials met prespecified statistical criteria for deciding the trials found something on their primaries. Qualitatively, the two trials showed much the same result on the primary end point. The placebo group, on average, improved a few meters at 4 weeks and was a few meters less than baseline at study end, while the active treatment groups showed improvements by week 4 that were at least sustained to the full period of follow-up. Subjects in Study 352 continued on blinded treatment out to 28 weeks. The change in walking distance was about 20% on 125 mg bid in Study 351 and 11% (125 mg bid) and 16% (250 mg bid) in Study 352. The largest changes in walking distance were seen in subjects with lower baseline walking distances.

Dr. Robbie has performed NONMEM analysis of 6-minute walk data from studies 351 and 352. This analysis is reproduced in the figure below.

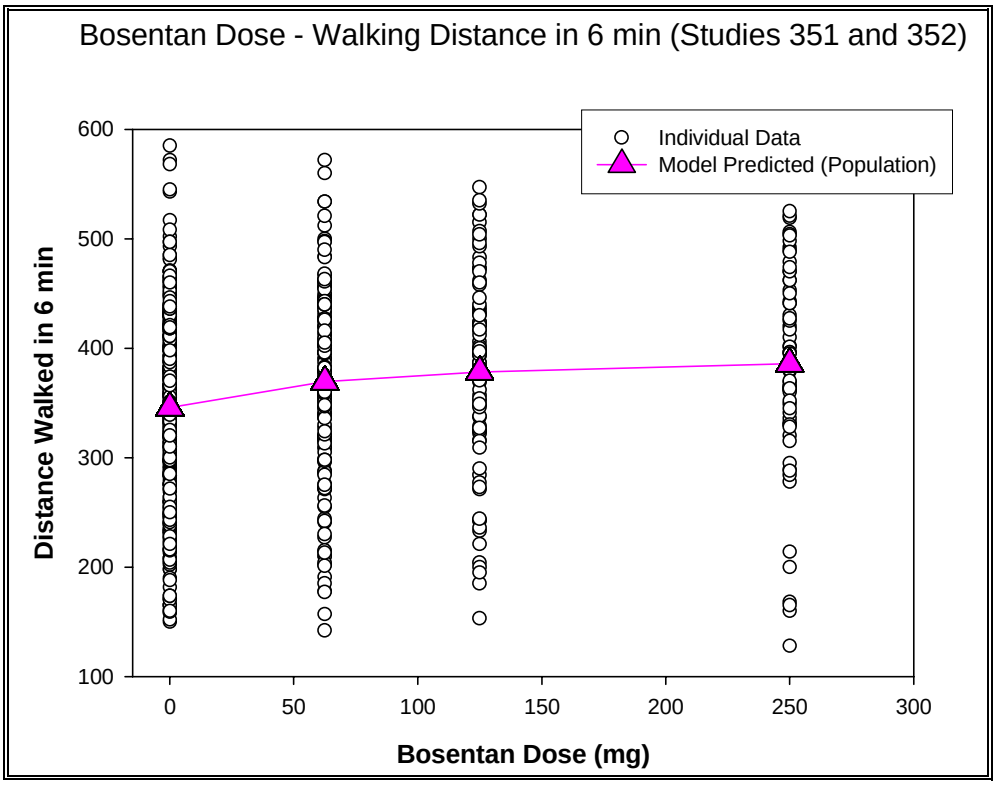

Figure 1. Analysis of dose-response

Two points can be made from this figure. One is that very little difference can be expected from doses of 125 and 250 mg[2]. The second is that the effect of treatment with bosentan, while unequivocal in a large population, will not be discernible in an individual patient.

Unlike the overall analysis, an analysis of walking distance by category of etiology is sensitive to the mode of handling early withdrawals, because 4 of the 5 subjects assigned a zero post-baseline walking distance came from the cohort with scleroderma. With these values included, this group has less of a treatment effect, but with them excluded from the analysis, there appears to be no effect of etiology.

Although there are no studies permitting titration during long-term treatment, tolerance or loss of effectiveness did not appear to be problems out to 28 weeks of placebo-controlled experience.

Supporting data came from the analyses of time to clinical worsening, which tended to be longer on bosentan, Borg dyspnea index, where the score rose (greater perceived exertion) on placebo and declined on bosentan, WHO functional class assessments, where improvement was more likely on bosentan than on placebo, and a trend for less need for additional therapy on bosentan.

Bosentan use was associated with reduction in blood pressure, -10.8/-8.6 mmHg in Study 351 and a smaller but directional similar change in Study 352. There is no

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[2] *Dr. Robbie modeled these data including or excluding subjects assigned a zero walking distance, assuming a normal or log-normal distribution, and with a linear or Emax model. Inclusion of subjects with a zero walking distance is a conservative approach to deciding if there is a treatment effect, but it inappropriate for estimating the magnitude of effect. The fits using a log-normal distribution were about 1% better than those with the normal distribution. After adjustment for the larger number of free parameters, the Emax model was about 20% better than the linear model. In general, this analysis confirms that the 250-mg dose is little better from the 125-mg dose.*

clinically significant effect on heart rate in either study. However, at doses up to 2000 mg/day, bosentan was scarcely distinguishable from placebo in effects on blood pressure in studies of essential hypertension.

Baseline and on-treatment invasive hemodynamic assessments are available for Study 351. The changes from baseline and placebo were PAP -6.7 mmHg, PVR -414, CI -1.0 L/min/m^2, RAP -6.2 mmHg, and PCWP -3.8 mmHg, all nominally statistically significant. These changes are consistent with the posited mechanism of action.

The safety database for bosentan is derived from about 250 subjects in controlled studies of pulmonary arterial hypertension and about 750 subjects in controlled trials for other indications, mostly chronic heart failure. The mean dose in the controlled studies overall was >1000 mg/day, but the maximum in studies of pulmonary hypertension was 250 mg bid. The mean duration was about 4 weeks in controlled studies generally, but it was more than 12 weeks in pulmonary hypertension.

Rates of withdrawal were similar in placebo and active treatment groups of all controlled studies, with the most common reasons for withdrawal being "sponsor's decision" (24%), adverse events (11%), and death (4%).

Worsening pulmonary hypertension was the attributed cause of death in the few deaths among bosentan subjects in pulmonary hypertension studies.

Serious adverse events have been reported in 8% of bosentan subjects in studies of pulmonary arterial hypertension. The most common adverse event associated with withdrawal was hepatic enzyme elevation, much more common on bosentan than on placebo. The database is simply too small to detect or exclude many other events that may be treatment related.

Elevations in AST or ALT to at least 3 times upper limit of normal occurred in about 10% of all subjects receiving bosentan; of these, about 1/3 had elevations to greater than 8 times upper limit of normal. Elevations in gamma GT were about as common, while elevations in bilirubin or alkaline phosphatase were much less common. An analysis the sponsor performed is suggestive that elevations in hepatic enzymes are weakly dose-related and infrequent in the first few weeks of treatment.

Individual case histories for hepatic enzyme elevations are described in Dr. Gordon's review. There are cases of positive rechallenge. In most cases, enzyme levels normalized when the study drug was terminated, although it is difficult to specify the time course for recovery. Liver enzyme elevations were sometimes accompanied by fever and abdominal pain.

The only other laboratory abnormalities with any likely relationship to bosentan were hematologic. About 5% of bosentan subjects had anemia as an adverse event, and about twice as many subjects had clinically significant reductions in hematocrit or hemoglobin. The drop in hemoglobin appears soon after exposure to bosentan, and it averaged about 1 g/dL with long-term exposure. One subject underwent bone marrow assessment which showed a normocellular marrow with adequate hematopoietic reserves. Some subjects were treated with packed red cells. Anemia was not associated with identified sites of hemorrhage.

Heart rate and ECG intervals were not significantly affected by bosentan.

Should bosentan be approved for the treatment of pulmonary arterial hypertension?

To its credit, bosentan was shown to be effective in improving walking distance in two prospective studies, for which walking distance was the primary end point. The magnitude of effect on walking distance was probably clinically meaningful, and it was accompanied by positive trends in other measures of symptomatic benefit.

On the other hand, symptomatic benefit is not an improvement in outcome. No trends with respect to outcome, positive or negative, can be discerned from the available data. Furthermore, inter- and intra-subject variability is large compared with the mean treatment effect, so physicians and patients will generally not be sure that changes in symptoms are attributable to treatment.

The improvement in symptoms carries with it numerous risks. They include teratogenicity, P450 enzyme interactions affecting concomitant medications, hepatotoxocity, and anemia. Although these risks did not result in clearly worsened outcome, it is difficult to draw much comfort given the small size of the safety database and the likely less aggressive monitoring that occurs in clinical practice.

The population studied with bosentan included primary pulmonary hypertension and pulmonary hypertension secondary to connective tissue or autoimmune diseases. The standards for approval should probably not be the same in these areas. Flolan (epoprostinol) is only indicated for treatment of primary pulmonary hypertension, where its considerable risks, primary related to mode of administration, do not overshadow a mortality benefit. One should consider whether bosentan delays the initiation of Flolan, and, if so, whether that is a good idea. There is no approved treatment for secondary pulmonary hypertension, so symptomatic improvement is clearly worth some risk.

Clearly, a case can be made for approval. Bosentan is effective in improving the exercise capacity in patients with pulmonary hypertension of various etiologies. This benefit was manifest in other indices of symptomatic improvement. The drug will need close monitoring, but irreversible harm can probably be prevented by appropriate surveillance.

A reasonable case can also be made against approval, particularly in primary pulmonary hypertension. Patients who receive the drug will never know whether their own symptoms are improved because of it, or how much worse they would feel off of it. They will incur real risks—from inadequate attention on the part of physicians to hepatic and hematologic effects or to drug interactions and from inadequate exploration of safety in the target population—for no certain gain. In terms of outcome—mortality or disease progression, the data say there is no benefit, but there may be irreversible harm in delaying the initiation of life-prolonging treatment.